PYRIDOSTIGMINE BROMIDE Tablets, USP
30 mg

Rx only

CAUTION!

PYRIDOSTIGMINE BROMIDE IS FOR USE AS A PRETREATMENT FOR EXPOSURE TO THE CHEMICAL NERVE AGENT SOMAN. PYRIDOSTIGMINE ALONE WILL NOT PROTECT AGAINST EXPOSURE TO SOMAN. THE EFFICACY OF PYRIDOSTIGMINE IS DEPENDENT UPON THE RAPID USE OF ATROPINE AND PRALIDOXIME (2-PAM) AFTER SOMAN EXPOSURE.

PRIMARY PROTECTION AGAINST EXPOSURE TO CHEMICAL NERVE AGENTS IS THE WEARING OF PROTECTIVE GARMENTS INCLUDING MASKS, HOODS AND OVERGARMENTS DESIGNED SPECIFICALLY FOR THIS USE.

INDIVIDUALS MUST NOT RELY SOLELY UPON PRETREATMENT WITH PYRIDOSTIGMINE AND THE ANTIDOTES ATROPINE AND PRALIDOXIME (2-PAM) TO PROVIDE COMPLETE PROTECTION FROM POISONING BY THE CHEMICAL NERVE AGENT SOMAN.

PYRIDOSTIGMINE MUST NOT BE TAKEN AFTER EXPOSURE TO SOMAN. IF PYRIDOSTIGMINE IS TAKEN IMMEDIATELY BEFORE EXPOSURE (E.G., WHEN THE GAS ATTACK ALARM IS GIVEN) OR AT THE SAME TIME AS POISONING BY SOMAN, IT IS NOT EXPECTED TO BE EFFECTIVE, AND MAY EXACERBATE THE EFFECTS OF A SUB-LETHAL EXPOSURE TO SOMAN.

FOR MILITARY COMBAT MEDICAL USE ONLY

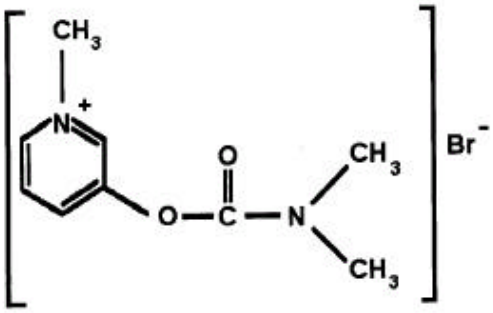
DESCRIPTION

Pyridostigmine bromide tablets, USP 30 mg. Pyridostigmine bromide is an orally active cholinesterase inhibitor. Its chemical name is: 3-hydroxy-1-methylpyridinium bromide dimethylcarbamate.

CAS registration number is *101-26-8.*

White tablet each imprinted with letters “PBT”.

Pyridostigmine bromide has a molecular formula of $C_9H_{13}BrN_2O_2$, a molecular weight of 261.12, and the following molecular structure:



The inactive ingredients included in the tablet formula are: colloidal silicon dioxide, lactose anhydrous, and stearic acid or, alternatively; lactose, starch, silica precipitated, talc, and magnesium stearate.

ANIMAL PHARMACOLOGY

Evidence of the effectiveness of pyridostigmine as a pre-treatment for Soman poisoning was obtained from studies in animals alone, because it is clearly unethical to perform such studies in humans. While the results of these animal studies cannot be extrapolated to humans with certainty, the extrapolation is supported by the reasonably well understood pathophysiologic mechanisms of the toxicity of Soman and the mechanism of the protective effect of pyridostigmine pre-treatment, as examined in various animal species. In addition, the results of these animal studies establish that pyridostigmine is reasonably likely to produce clinical benefit in humans. The section below explains the current understanding of the mechanism of Soman toxicity and the beneficial effect of pyridostigmine pre-treatment, as well as the basis for extrapolating the animal findings to humans.

Pyridostigmine pretreatment has been shown in animals to decrease the lethality of the nerve agent Soman, provided atropine and pralidoxime (2-PAM) are administered immediately after exposure to Soman. The mechanism of Soman induced death is reasonably well-understood; death is believed to result primarily from respiratory failure due to irreversible inhibition of the enzyme acetylcholinesterase and the consequent increase in the level of the neurotransmitter acetylcholine 1) at nicotinic receptors at the neuromuscular junction, resulting in pathological stimulation and ultimate failure of the muscles of respiration, 2) at muscarinic receptors in secretory glands and smooth muscle, resulting in excessive respiratory secretions and bronchoconstriction, and 3) at cholinergic receptors in the brain, resulting in central respiratory depression. The effect of pyridostigmine is presumed to result from its reversible inhibition of a critical number of

acetylcholinesterase active sites in the peripheral nervous system, protecting them from irreversible inhibition by Soman. (Pyridostigmine is not thought to enter the brain in significant amounts.) When the pyridostigmine-induced inhibition of the enzyme is subsequently reversed, there is a small residual amount of enzyme activity that is adequate to sustain life (provided atropine and 2-PAM are subsequently administered). An implication of this presumed mechanism is that it is not helpful to give pyridostigmine either just before or during exposure to Soman.

Rhesus monkeys were given oral doses of pyridostigmine every 8 hours for a total of 6 doses, and were challenged with Soman given intramuscularly 5 hours after the last pyridostigmine dose. Two dosage groups of pyridostigmine were used: a low dose group given 1.2 mg/kg for all 6 doses, and a high dose group given 1.2 and 1.8 mg/kg for the first and second doses, respectively, and 2.4 mg/kg for the final 4 doses. These animals were also given atropine and 2-PAM after exposure to Soman. An untreated control group, and a group given atropine and 2-PAM (but not pyridostigmine), were also used. The primary endpoint in this study was a decrease in the lethality of Soman expressed as an increase in the LD 50 (the dose of Soman that killed 50 % of the animals). The atropine/2-PAM control group showed a small but statistically significant 1.6 fold increase in the Soman LD 50 compared to the untreated control group. The groups given pyridostigmine as well as atropine and 2-PAM showed increases in the Soman LD50 of at least 40 fold compared to the untreated control group and at least 25 fold compared to the atropine/2-PAM group. The two dose levels of pyridostigmine showed similar effectiveness.

Additional studies in rhesus monkeys and guinea pigs also showed effectiveness of pyridostigmine (in the presence of post-Soman administration of atropine and 2-PAM). The magnitude of effect in guinea pigs was smaller than that in monkeys (Soman LD 50 increased 4-7 fold compared to untreated control and 2-4 fold compared to atropine/2-PAM alone). Pyridostigmine produced only small and inconsistent effects in studies in rats, mice and rabbits. It is thought that the effect of pyridostigmine in rats and mice is masked by high blood levels of the enzyme carboxylesterase, which eliminates Soman from blood and makes those species highly resistant to Soman. In a study in which rats were given an inhibitor of carboxylesterase, pretreatment with pyridostigmine plus atropine increased the LD 50 of Soman 8.5 fold compared to untreated controls. Humans have little or no carboxylesterase in blood.

Animal studies have shown that pyridostigmine pretreatment was effective only when animals were given atropine and 2-PAM after exposure to Soman.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Pyridostigmine bromide is poorly absorbed from the gastrointestinal tract with an absolute bioavailability of 10-20%. Following a single oral dose of 30 mg pyridostigmine

bromide in the fasting state, the TMAX was 2.2 ± 1.0 hours. The pharmacokinetics of pyridostigmine bromide is linear over the dose range of 30-60 mg. Following multiple doses of pyridostigmine bromide (30 mg every 8 hours for 21 days), the average steady-state trough concentration of pyridostigmine was about ¼ of the peak concentration after a single dose.

The volume of distribution was about 19 ± 12 liters, indicating that pyridostigmine distributes into tissues. No information on protein binding of pyridostigmine is available.

Pyridostigmine undergoes hydrolysis by cholinesterases and is metabolized in the liver. It is excreted in the urine both as unchanged drug and its metabolites. The systemic clearance of pyridostigmine bromide is 830 mL/min and the elimination half-life of pyridostigmine bromide is approximately 3 hours.

Renal Dysfunction

In anephric patients (n=4), the elimination half-life increased 3 fold and the systemic clearance decreased by 75%. Therefore caution should be observed when administering pyridostigmine bromide to patients with impaired renal function.

Hepatic Impairment

No information is available on the pharmacokinetics of pyridostigmine in hepatic impaired patients.

Gender

The clearance of pyridostigmine bromide is not influenced by gender.

Elderly

In a pyridostigmine study in the elderly (71-85 years), the elimination half-life of pyridostigmine was similar to the half-life in the young (21-51 years). However, the systemic plasma clearance was 30% lower in the elderly.

INDICATIONS AND USAGE

Pyridostigmine bromide is indicated for prophylaxis against the lethal effects of soman nerve agent poisoning. Pyridostigmine is intended to be used in conjunction with protective garments, including a gas mask, and immediate atropine and pralidoxime therapy at the first sign of nerve agent poisoning. Pyridostigmine should be stopped at the first sign of nerve agent poisoning.

The evidence for the effectiveness of pyridostigmine as prophylaxis against Soman-induced toxicity was derived from animal studies alone. (see ANIMAL PHARMACOLOGY)

CONTRAINDICATIONS

Pyridostigmine bromide is contraindicated in mechanical intestinal or urinary obstruction.

Do not administer to personnel with known hypersensitivity to anticholinesterase agents

WARNINGS (see CAUTION at beginning of this label)

Pyridostigmine pretreatment offers no benefit against the nerve agent Soman unless the nerve agent antidotes atropine and pralidoxime are administered once symptoms of poisoning appear. Pyridostigmine should be discontinued at the first sign of nerve agent poisoning since it may exacerbate the effects of a sub-lethal exposure to Soman.

Pyridostigmine should be used with caution in patients with bronchial asthma, chronic obstructive pulmonary disease, bradycardia, cardiac arrhythmias, and people being treated for hypertension or glaucoma with beta adrenergic receptor blockers.

Caution should be taken when administering pyridostigmine bromide to individuals with known bromide sensitivity. The risks and benefits of administration must be weighed against the potential for rash or other adverse events in these individuals.

PRECAUTIONS

General

If personnel experience serious side effects such as difficult breathing, severe dizziness, or loss of consciousness as a result of ingestion of pyridostigmine bromide, they should be advised to temporarily discontinue use of product and seek immediate medical attention. Serious adverse events should be reported to their commander and responsible medical officer.

Information for Patients

See Patient Information Sheet.

Drug Interactions

A potential interaction between the antimalarial drug mefloquine and pyridostigmine bromide exists through a possible additive effect on the gastrointestinal tract. The most common complaint about both drugs is loose bowels. It has been reported that simple additive effects on the atrial rate occur when mefloquine and pyridostigmine bromide are combined.

Because anticholinesterase drugs are often used in the treatment of glaucoma, the use of pyridostigmine bromide in such situations may have an additive effect that may cause or exacerbate problems with night vision.

The bradycardia associated with the use of narcotics may exacerbate pyridostigmine-induced bradycardia.

Particular caution should be observed in the administration of depolarizing neuromuscular blocking agents (e.g., succinylcholine) during surgery since the degree of neuromuscular blockade that ensues may be enhanced by previously administered pyridostigmine bromide. Doses of non-depolarizing neuromuscular blocking agents (e.g., pancuronium bromide) may need to be increased in patients previously administered pyridostigmine. Atropine antagonizes the muscarinic effects of pyridostigmine, and this interaction is utilized to counteract the muscarinic symptoms of pyridostigmine toxicity. Anticholinesterase agents are sometimes effective in reversing neuromuscular block induced by aminoglycoside antibiotics. However, aminoglycoside antibiotics, local and some general anesthetics, antiarrhythmic agents, and other drugs that interfere with neuromuscular transmission should be used cautiously, if at all. Theoretically, drugs such as dexpanthenol, which are converted to pantothenic acid *in vivo,* may have additive effects with pyridostigmine by increasing production of acetylcholine.

Carcinogenesis, Mutagenesis, Impairment Of Fertility

Carcinogenicity: No long-term studies to evaluate carcinogenicity have been performed in animals.

Mutagenicity: Pyridostigmine was mutagenic and clastogenic in an *in vitro* mammalian gene mutation assay in mouse lymphoma cells, in the presence of metabolic activation only. Pyridostigmine was not mutagenic in an *in vitro* bacterial reverse mutation assay (Ames Test) and in an *in vitro* mammalian gene mutation assay in Chinese hamster ovary cells, and was not clastogenic in an *in vitro* assay in Chinese hamster ovary cells or in an *in vivo* mouse micronucleus assay.

Impairment of Fertility: Pyridostigmine did not impair fertility in male and female rats given oral doses of up to 45 mg/kg/day (5 times the recommended human daily dose of 90 mg on a mg/m^2 basis) beginning at 10 (males) or 2 (females) weeks prior to mating.

Pregnancy *Pregnancy Category B*

Pyridostigmine produced no teratogenic effects in rats given up to 30 mg/kg/day and in rabbits given up to 45 mg/kg/day orally during the period of organogenesis. These doses are 3 and 10 times, respectively, the recommended human dose of 90 mg on a mg/m^2 basis. In rats, a slight degree of delayed skeletal ossification was seen at 30 mg/kg, a dose which caused maternal toxicity, and a slight increase in the incidence of hydronephrosis was seen at all dose levels (lowest dose tested was 3 mg/kg). In rabbits, a slight increase in the incidence of hydronephrosis was seen at 45 mg/kg, a dose which caused maternal toxicity, and increased incidences of blood vessel variations were seen at all doses (lowest dose tested was 5 mg/kg). There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk caution should be exercised when pyridostigmine is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of pyridostigmine did not contain sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In the elderly (71-85 years of age) the elimination half-life, volume of distribution (central and steady state) were comparable with the young (21-51 years of age). However the systemic plasma clearance was significantly lower in the elderly compared to the young (6.7 ± 2.2 vs. 9.5 ± 2.7 ml/min/kg).

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

The side effects of pyridostigmine bromide are typically of two varieties, muscarinic and

nicotinic. Muscarinic side effects include abdominal cramps, bloating, flatulence, diarrhea, emesis, increased peristalsis, nausea, hypersalivation, urinary incontinence, increased bronchial secretion, diaphoresis, miosis, and lacrimation. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculations, and weakness.

Pyridostigmine is a quaternary ammonium compound and does not readily cross the blood-brain barrier. Compared to the peripheral effects of pyridostigmine bromide, central nervous system manifestations are less frequent and less serious, primarily consisting of headache and vertigo, with minor and clinically insignificant changes in heart rate, blood pressure, and respiratory function.

Extremely high doses may produce CNS symptoms of agitation, restlessness, confusion, visual hallucinations, and paranoid delusions. Electrolyte abnormalities, possibly resulting from high serum bromide concentrations, also have been reported. Death may result from cardiac arrest or respiratory paralysis and pulmonary edema.

In a controlled study of 90 healthy volunteers comparing pyridostigmine 30 mg every 8 hours to placebo for 21 days, the following incidence of adverse events was reported.

Table 1: Incidence of Adverse Events – 2%

Event:	**% Pyridostigmine N = 60**	**% Placebo N = 30**
Diarrhea	7	0
Abdominal Pain	7	0
Dysmenorrhea	5	0
Twitch	3	0
Myalgia	2	0
Dry Skin	2	0
Urinary Frequency	2	0
Epistaxis	2	0
Amblyopia	2	0
Hypesthesia	2	0
Neck Pain	2	0

Other less common adverse events seen during controlled and uncontrolled clinical trials for pyridostigmine include the following:

- *Pulmonary:* Exacerbation of acute bronchitis and asthma
- *Cardiovascular:* Elevated blood pressure, decreased heart rate (4-6 beats per minutes), chest tightness
- *Eyes:* Change in vision, eye pain
- *Neurologic:* Headache, hypertonia, difficulty in concentrating, confusion, disturbed sleep, tingling of extremities, numbness of the tongue
- *Skin:* Increased sweating, rash, alopecia
- *Digestive:* Vomiting, borborygmi, nausea, bloating, flatulence
- *General:* Warm sensation, lethargy/drowsiness, depressed mood

During safety studies at the recommended dosage, there were two reports of loss of consciousness, one of which also included urinary and fecal incontinence, stiffness of the upper torso and arms, post syncopal skin pallor, post syncopal confusion, and post syncopal weakness (suggesting a seizure event).

As with any compound containing bromide, a skin rash may be observed in an occasional patient, which usually subsides promptly upon discontinuance of the medication.

DRUG ABUSE AND DEPENDENCE

Although the abuse potential of pyridostigmine has not been specifically assessed, no abuse of, tolerance to, withdrawal from, or drug-seeking behavior was observed in patients who received pyridostigmine in clinical trials. Cholinesterase inhibitors are not believed to be associated with drug abuse.

OVERDOSAGE

As is true of all cholinergic drugs, overdosage of pyridostigmine bromide may result in cholinergic crisis, a state characterized by increasing muscle weakness that, through involvement of the muscles of respiration, may lead to death. Overdosage with pyridostigmine must be differentiated from the acute manifestations of nerve agent poisoning which may also be characterized by a cholinergic crisis. Atropine should be used to treat pyridostigmine overdosage.

In the treatment of pyridostigmine overdosage, maintaining adequate respiration is of primary importance. Tracheostomy, bronchial aspiration, and postural drainage may be required to maintain an adequate airway; respiration can be assisted mechanically if required. Supplemental oxygen may be necessary. Pyridostigmine should be discontinued immediately and 1-4 mg of atropine sulfate administered i.v. Additional doses of atropine may be given every 5-30 minutes as needed to control muscarinic symptoms. Atropine overdosage should be avoided, as tenacious secretions and bronchial plugs may result. It should be kept in mind that unlike muscarinic effects, the skeletal muscle effects and consequent respiratory paralysis (nicotinic effects) which can occur following pyridostigmine overdosage are not alleviated by atropine.

DOSAGE AND ADMINISTRATION

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The dose of pyridostigmine is one 30 mg tablet every 8 hours to be started at least several hours prior to exposure to Soman. At the first sign of nerve agent poisoning, pyridostigmine should be discontinued and treatment with atropine and pralidoxime should be instituted immediately.

There is no known advantage to taking pyridostigmine just prior to or concurrent with Soman exposure. According to the mechanism of action of pyridostigmine described above (see ANIMAL PHARMACOLOGY section), pyridostigmine should be effective when it is given sufficiently in advance of Soman poisoning to provide a pool of protected enzyme. Therefore, it is expected that pyridostigmine will not be effective if administered just prior to or during exposure to Soman.

The effects of use beyond 14 consecutive days have not been definitively established, therefore, continued use beyond 14 consecutive days should be evaluated in the context of the likelihood of exposure to Soman nerve agent.

HOW SUPPLIED

NSN 6505-01-178-7903 * Immediate Container. Twenty-one (21) tablets individually sealed in a blister or strip package which is supplied in a protective sleeve.

*The NSN refers to the actual unit that is ordered from supply (if someone orders 1 of this stock number they will get one mylar bag as a unit of issue (or one package of 10 blister packs). The exterior carton lists the NSN and the description of the product that the NSN applies to and lists 10 PG (packages) as the quantity within the carton.

STORAGE

Store refrigerated between 2 and 8 ^{0}C (36-46 ^{0}F). Protect from light.

Do not dispense the content of unit packages (10 blister packs) and shipping containers (10 packages of 10 each blister packs) after removal from refrigeration for more than a

total of 3 months. Do not use after the 10 year expiration date provided on the package. Military personnel should be advised to discard the contents of the individual unit packages of pyridostigmine 3 months after issue.

For Military Use Only

Distributed by: Defense Supply Center, Philadelphia
Medical Directorate
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For: Office of The Surgeon General
U.S. Army Medical Research
and Materiel Command (MCMR-RCQ-RA)
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